AMENDMENTS TO THE SPECIFICATION

In the specification, at page 6, lines 24-33, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

In addition to the new immunization and screening techniques provided herein, antibodies that bind to aminophospholipids and anionic phospholipids and have a number of advantageous properties can now be identified by competition and/or functional assays using the monoclonal antibodies 1B9, 1B12, 3B10, 2G7, 7C5, 9D2 or 3G4. Currently, the 1B12, 3B10, 9D2 and 3G4 antibodies are preferred~~, as these antibodies do not require serum for phospholipid binding~~. The monoclonal antibodies 9D2 and 3G4 are more preferred, with monoclonal antibody 3G4 (ATCC 4545) currently being the most preferred. To identify additional antibodies that compete with any of the foregoing antibodies, preferably 3G4, the preferred assays are currently competition assays based upon an ELISA, a number of which are described herein, and working examples of which are disclosed.

In the specification, at page 9, lines 18-27, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

In certain aspects, the antibodies will effectively compete with the monoclonal antibody 1B9, 1B12, 3B10, 2G7, 7C5, 9D2 or 3G4, preferably with 9D2 or 3G4, and most preferably with 3G4 (ATCC 4545), for binding to an aminophospholipid or anionic phospholipid, preferably PS, or will have the aminophospholipid or anionic phospholipid binding profile of the monoclonal antibody 1B9, 1B12, 3B10, 2G7, 7C5, 9D2 or 3G4, preferably of 9D2 or 3G4, and most preferably of 3G4, as set forth in Table 4; ~~and will not be serum dependent, *i.e.*, will not require serum to bind to the aminophospholipid or anionic phospholipid;~~ not be derived from a patient with a disease, and will not significantly inhibit coagulation reactions *in vitro*, cause significant thrombosis *in vivo* or have lupus anticoagulant activities.

In the specification, at page 24, lines 12-15, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

All selection criteria~~, as used herein,~~ are preferably conducted in the absence of serum, to avoid the drawbacks with generating antibodies that could mimic the pathological antibodies of patients, which bind to aminophospholipids or anionic phospholipids in conjunction with proteins.

In the specification, at page 79, lines 24-30, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

~~The~~ Certain of the antibodies of the present invention have been particularly selected on the basis of not binding to aminophospholipids and anionic phospholipids in combination with protein cofactors, but rather are "true" anti-phospholipid antibodies. ~~As such, the~~ The antibodies of the invention do not ~~bind or~~ displace the protein cofactors from the phospholipids and are therefore safe for administration. Indeed, mice treated with the antibodies of the invention at high doses for prolonged periods showed no changes in coagulation capability, yet mice respond with APS when injected with anticardiolipin or lupus anticoagulant antibodies.

In the specification, at page 80, lines 18-25, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

In order to generate antibodies to aminophospholipids and anionic phospholipids with advantageous properties and/or reduced or essentially no side effects, the present invention provides preferred immunization and screening methods. Other immunization techniques and antibodies have been reported in the literature (Umeda *et al.*, 1989; Igarashi *et al.*, 1991; Rote *et al.*, 1993), including those with reported specificity for the type of fatty acid chains involved (Levy *et al.*, 1990; Qamar *et al.*, 1990). However, the present immunization techniques~~, and particularly the selection of antibodies that are not serum dependent, provides~~ provide particular benefits.

In the specification, at page 81, lines 2-6, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The antibodies of the invention also have the advantage of recognizing all or most anionic phospholipids, which can provide more targets for binding. Therefore, the second generation antibodies of the invention can be defined as having substantially the same, or the same, phospholipid specificity as the 9D2 or 3G4 (ATCC 4545) antibodies, as disclosed herein in Table 4~~, and as not being serum dependent~~.

In the specification, from page 81, line 32 to page 82, line 4, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The antibodies of the present invention can also be characterized by their affinity. Prior to the invention, the antibodies in the literature had relatively weak affinity (where reported). In certain embodiments, the second generation antibodies of the invention are therefore defined as those that have an affinity for PS of at least equal to the affinity of the 9D2 or 3G4 (ATCC 4545) antibodies for PS, in particular, the affinity when measured in an ELISA as described herein, as disclosed in Table 3~~, and as not being serum dependent~~.

In the specification, at page 82, lines 6-13, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

More preferably, the second generation antibodies of the invention are defined as those having an affinity for PS of at least equal to the affinity of the 9D2 or 3G4 (ATCC 4545) antibodies for PS, as disclosed in Table 3, and as having substantially the same, or the same, phospholipid specificity as the 9D2 or 3G4 (ATCC 4545) antibodies, as disclosed in Table 4~~, and as not being serum dependent~~. Most preferably, the second generation antibodies are those having an affinity for PS of at least equal to the affinity of the 3G4 (ATCC 4545) antibody for PS, as disclosed in Table 3, and as having the same phospholipid specificity as the 3G4 (ATCC 4545) antibody, as disclosed in Table 4~~, and as not being serum dependent~~.

In the specification, from page 202, line 24 to page 203, line 2, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The pathogenic anti-phospholipid antibodies that circulate in patients with antiphospholipid syndrome are believed to bind to PS, PE and other phospholipids in combination with proteins, such as β_2-glycoprotein I, prothrombin, kininogens, prekallikrein and factor XI (Rote, 1996; Sugi and McIntyre, 1995; 1996a; 1996b). β_2-glycoprotein I and prothrombin bound to PS are reported to be the primary antigens for anti-cardiolipin antibodies and lupus antibodies, respectively. ~~The~~ Certain of the antibodies of the present invention have been particularly selected on the basis of not binding to aminophospholipids and anionic phospholipids only in the presence of serum proteins. ~~Therefore, by binding to the phospholipid component, the~~ The antibodies of the invention are contemplated for use in antagonizing or competing with the pathogenic antibodies in such patients, thus displacing the pathogenic antibodies from their phospholipid-protein targets in the body.

In the specification, at page 241, lines 20-26, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

An important aspect of the inventors' technique to prepare monoclonal antibodies useful in tumor treatment is the selection strategy, which involves screening to select antibodies that bind to aminophospholipids or anionic phospholipids, but not to neutral phospholipids. ~~Another important~~ A certain aspect is to select antibodies that bind to PS-coated plates as strongly in the presence of serum as in the absence of serum. ~~This is carried out to exclude antibodies that recognize complexes of PS and serum proteins, which are believed to cause or contribute to anti-phospholipid syndrome.~~

In the specification, at page 243, in Table 2, please delete the existing table and replace the deleted table with the following table after making the following changes:

TABLE 2

Isotype and Serum-Dependence of Anti-PS Antibodies

Name	Origin	Species/Isotype	Serum-dependence
3SB	Rote *et al.*, 1993	Mouse IgM kappa	None
D11	N. Rote	Mouse IgM kappa	
BA3	Rote *et al.*, 1993	Mouse IgM kappa	
9D2	This study	Rat IgM kappa	None
1B12	This study	Mouse IgG_1 kappa	
3G4	This study	Mouse IgG_3 kappa	~~None~~ Yes
1B9	This study	Mouse IgG_1 kappa	Absolute
3B10	This study	Mouse IgG_3 kappa	~~None~~ Yes
2G7	This study	Mouse IgG_1 kappa	Absolute
7C5	This study	Mouse IgG_1 kappa	Absolute

In the specification, at page 246, lines 10-16, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The 1B9, 2G7 and 7C5 antibodies behave essentially the same. These antibodies recognize only PS and require serum or serum proteins for binding to PS. The binding of 1B9, 2G7 and 7C5 to various phospholipids was assayed only in the presence of 10% bovine serum~~, whereas binding of the other antibodies was tested either in the absence or in the presence of serum~~. For ~~antibodies other than 1B9, 2G7 and 7C5~~ the 9D2 antibody, the presence of serum does not change preference in binding to a particular phospholipid. ~~This latter group, including 3G4, 3B10 and 9D2, have the preferred property of binding~~ The 9D2 antibody binds to PS in the absence of serum.

In the specification, at page 302, lines 17-22, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The ~~epitope recognized by 3G4 appears to lie within the~~ phosphoglycerol core of the anionic phospholipids~~, which~~ is the same in phospholipids from all mammalian species. The 3G4 antibody ~~thus~~ reacts with both mouse and human phospholipids, which is important for pre-clinical and clinical development. 3G4 is more specific for anionic phospholipids than the natural ligand, annexin V. Unlike 3G4, annexin V also binds strongly to neutral phospholipids in physiological concentrations of Ca^{2+}.

In the specification, at page 306, lines 2-7, please delete the following paragraph:

An important aspect of the 3G4, 9D2 and like antibodies stems from the inventors' realization that desirable antibodies should preferably be selected using a screen to identify antibodies that bind to PS-coated plates as strongly in the presence of serum as in the absence of serum. This new development provides the ability to identify and exclude antibodies that recognize complexes of PS and serum proteins, as such complexes are believed to be the cause of, or an important factor in, anti-phospholipid syndrome and associated pathologies.